PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference 01-ST-02-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IT 03/00011	International filing date *(day/month/year)* 15.01.2003	Priority date *(day/month/year)* 15.01.2002
International Patent Classification (IPC) or both national classification and IPC C07C323/52, C07C323/52		
Applicant SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.07.2003	13.04.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer English, R Telephone No. +31 70 340-2860

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IT 03/00011

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-48 as originally filed

Claims, Numbers

1-7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-5 (in part)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-5 (in part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-7
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-7
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The International Search Report was incomplete with respect to a part of the subject-matter of claims 1-5. It covered only the compounds of the examples and their medicinal use other than those responding to PPARα activation. Consequently, it is not possible to carry out a full International Preliminary Examination of claims 1-5 (Rule 66.1(e) PCT). The search report was complete for use of compounds of claim 1 in the treatment of diseases responding to PPARα activation and in the treatment of heart failure, hyperlipidaemia and atherosclerosis, and consequently the present examination is complete for the whole scope of claims 6,7.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: P.J. Brown, et al., Journal of Medicinal Chemistry, 1999, 42(19), 3785-3788 (XP002128791)
D2: DE 199 40 415 A (F. Spener) 8 March 2001
D3: D.A. Brooks, et al., Journal of Medicinal Chemistry, 2001, 44(13), 2061-2064 (XP002184099)
D4: GB 1 422 679 A (Funai Pharmaceutical Industries) 28 January 1976
D5: D.J. Abraham, et al., Journal of Medicinal Chemistry, 1984, 27(8), 967-978 (XP002024764)
D6: W.A. Denny, et al., Journal of Medicinal Chemistry, 1982, 45(3), 276-315 (XP002250593)
D7: R.S. Radad, et al., Journal of Medicinal Chemistry, 1991, 34(2), 752-757 (XP002250594)
D8: I. Lalezari, et al., Journal of Medicinal Chemistry, 1989, 32(10), 2352-2357 (XP002250595)
D9: S.T. Hazeldine, et al., Journal of Medicinal Chemistry, 2001, 44(11), 1758-1776 (XP002250596)
D10: I. Sircar, et al., Journal of Medicinal Chemistry, 1983, 26(7), 1020-1027 (XP001064059)
D11: J. Wrobel, et al., Journal of Medicinal Chemistry, 1998, 41(7), 1084-1091

(XP001124338)

D12: W.D. Crow, et al., Australian Journal of Chemistry, 1979, 32(1), 111-121 (XP008020680)

1. **Subject-matter**

The present application discloses phenoxy- and phenylthioacetic acid and derivatives thereof which are useful in the treatment of diseases responding to PPARα activation, such as heart failure, hyperlipidaemia and atherosclerosis.

2. **Novelty**

The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of claims 1-7 is not new.

2.1 Documents D1-D3 disclose various compounds falling within the scope of formula (I) of claim 1 all with PPARα activating activity:

D1: Bezafibrate, a compound falling within the scope of formula (I) of the present application, is shown (table 1) to have moderate activity in activating PPARα receptor sites.

D2: Bezafibrate, a potent hypolipidaemic compound (column 2, lines 65-68), is shown (figure 1; column 2, lines 65-68) to have moderate activity in activating PPARα receptor sites.

D3: Compounds 4-8 are 4-(2-(phenyloxazol)ethoxy)phenoxyacetic acid derivatives and therefore fall within the scope of formula (I) of the present application. These compounds are shown (table 1) to have measurable activity in activating PPARα.

Consequently, the subject-matter of claims 1-7 cannot be considered to be novel over that of D1-D3.

2.2 Document D4 discloses compounds (formula (I), examples 1,3-10,12-16,19) which are said to be active in the reduction of the level of cholesterol in the blood (page 1, lines 20-23). These compounds are thus useful in the treatment of a particular hyperlipidaemia (namely, hypercholesterolaemia) which the applicant admits is a disease "responding to PPARα activation" (page 6, lines 17-21). Consequently, the subject-matter of claims 1-7 cannot be considered to be novel over that of D4.

2.3 Documents D5-D11 also disclose compounds and some with use in the medical field and some with use in the treatment of the diseases listed in present claim 7 (see the

International Search Report for details). Consequently, the subject-matter of claims 1-5 cannot be considered to be novel over that of D5-D11.

Furthermore, according to the International Searching Authority, this cannot be considered to be an exhaustive list of compounds in the prior art falling within the scope of claims 1-5.

3. **Inventive step**

3.1 Documents D1-D3 describe compounds and their use in the treatment of diseases responding to activation of PPARα falling within the scope of claims 1-7 (see paragraph 2.1 above), i.e. these compounds are used in the prior art to solve the same problem as in the present application. Thus, the subject-matter of claims 1-7 does not involve an inventive step and does not satisfy the criterion set forth in Article 33(3) PCT.

3.2 As explained above, the present application lacks novelty and an inventive step. There is also a technical lack of unity between the various groups of compounds in the present application (Rule 13 PCT) since the common concept linking all these compounds, namely the phenyl-Y-C-CO-X group, is also present in the compounds of D1-D4 being used for the same purpose. This lack of unity will not be raised at this stage.

3.3 Document D1 is regarded as being the closest prior art to the subject-matter of claims 1-7, in so far as they are novel (see paragraph 3.2 above), and discloses bezafibrate as an activator of PPARα (table 1).

The applicant presents pharmacological data relating to some of the compounds of his invention in table 1 on page 45 and table 2 on page 47. However, it is not possible to compare these data with the data given in D1 for the PPARα agonist activity of bezafibrate. The present application does not contain such comparison data either. It is not possible what technical effect is achieved by the use of the novel compounds of claim 1 as agonists of PPARα.

The problem solved by claims 1-7 of the present application, in so far as they are novel, may therefore be regarded as the provision of alternative compounds which are useful in the treatment of diseases responding to PPARα activation. The applicant solves this problem by the use of the novel compounds of claim 1.

Only minor structural changes to compounds of D1-D3 are necessary to prepare some of the novel compounds of the present application. Such structural changes are considered normal in the art of medicinal chemistry as a means of producing alternative pharmaceutically active compounds. The person skilled in the art would expect that in making these changes the PPARα agonist activity would also be present in the newly prepared compounds and that they would be useful in the treatment of hyperlipidaemia.

Consequently, claims 1-7, in so far as they are novel, cannot be considered to involve and inventive step and do not satisfy the requirements of Article 33(3) PCT.